REMARKS

Entry of the foregoing amendments and favorable consideration of the subject application are respectfully requested in view of the following comments.

Claims 4 and 29-32 are currently pending. Claim 4 has been amended and claim 29 has been cancelled. Accordingly, claims 4 and 30-32 are presented herein.

Claim 4 has been amended to specify the HMG-CoA reductase inhibitor as being "selected from the group consisting of atorvastatin and rosuvastatin" which are found in the specification as filed at page 17, lines 1-10. Concurrently with this amendment, claim 29, which recited a larger group of HMG-CoA reductase inhibitors has been cancelled.

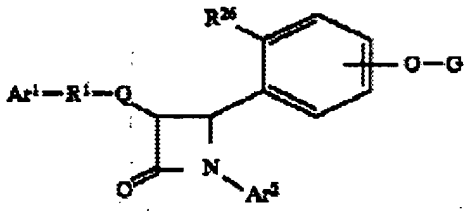
This amendment to claim 4 renders the scope of that claim, and all dependent claims, commensurate with the evidence provided in the previously filed declaration of Kazuhiro Kosakai and Applicants respectfully submit that any objection thereto has been overcome.

Applicants respectfully submit that the foregoing amendments are fully supported by the application as originally filed and neither add new matter nor expand the scope of the claims presented herein and that these amendments are properly in condition for entry at this time.

Applicants respectfully submit that the foregoing amendments place the application in condition for allowance.

Rejection of Claims Under 35 U.S.C. §103(a)

The Office Action rejects claims 4 and 29-32 under 35 U.S.C. § 103(a) as being unpatentable over Yumibe et al. (U.S. 5,756,470, May 26, 1998, of record) and Tomiyama et al. (U.S. 2004/0063929, April 1, 2004, PTO-1449 submitted April 25, 2006, English equivalent of WO02/066464, published August 29, 2002, of record). The Office Action states:

> "Yumibe et al teaches a combination of a cholesterol biosynthesis inhibitor and a β-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis [see abstract]. Suitable HMG CoA reductase inhibitors include lovastatin, pravastatin, fluvastatin and simvastatin [column 10, lines 24-27 and claim 17]. The genus of compounds taught by Yumibe et al. is as follows [column 2]:
>
> 
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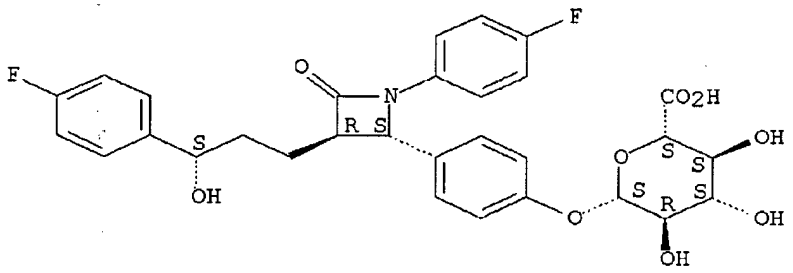
>
> Wherein R^{26} is H or O-sugar, G is a sugar, and Ar^1 and Ar^2 are aryl or substituted aryl. Specific embodiments are claimed in claim 13 and include the following:

L2 ANSWER 26 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 190448-57-8 REGISTRY
ED Entered STN: 27 Jun 1997
CN β-D-Glucopyranosiduronic acid, 4-[(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-oxo-2-azetidinyl]phenyl (CA INDEX NAME)

OTHER NAMES:
CN Sch 58235 glucuronide
CN Sch 60663
FS STEREOSEARCH
MF C30 H29 F2 N O9
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, PROUSDDR, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



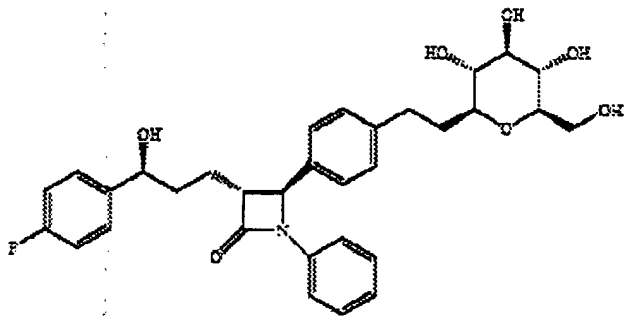
Pharmaceutical compositions comprising the compounds of Yumibe et al, and a lovastatin, pravastatin, fluvastatin, or simvastatin are specifically claimed [claims 17].

The pharmaceutical compositions can be administered in forms such as capsules, tablets, powders, etc., and can include excipients such as fillers, binders, buffers, etc. [column 17, lines 11-23]. The daily dose of the compound is about 0.001-30 mg/kg per day [column 17, lines 24-26]. The daily dose of the HMG reductase inhibitor administered in combination with the compound is 0.1-80 mg/kg per day in single or divided doses [column 17, lines 33-41]. The components may be administered separately [column 17, lines 49-51].

The difference in the beta-lactams taught by Yumibe et al. and the instantly claimed beta-lactams is that the instantly claimed lactams comprise C-glycosides and those of Yumibe et al. comprise O-glycosides.

Tomiyama et al teach beta-lactam compounds which are useful as serum cholesterol lowering agents [see abstract]. One preferred compound, compound 56 [page 18], shown below, is the same compound as that which is recited in instant claim 4:

56



Hypocholesterolemic beta-lactam-O-glucuronic acid conjugate derivatives are known, but the O-glycoside bonds in beta-lactam-O-glucuronate compounds can be hydrolyzed in the small intestine, possibly reducing the activity of the compounds [0003-0004]. Thus, hybrid beta-lactams having a C-glycoside, which is stable to metabolism by glycosidase and hydrolysis, were prepared [column 2, lines 3-10]. The compounds are excellent hypocholesterolemic agents and are expected to have reduced side effects compared to the O-glycoside compounds [0006].

Tomiyama et al. do not teach a combination of beta-lactam and HMG-CoA reductase inhibitor.

It would have been obvious to one of ordinary skill in the art to prepare a cholesterol-lowering composition comprised of a HMG-reductase inhibitor and a β-lactam taught by Tomiyama et al. The combination of beta-lactam cholesterol absorption inhibitor and HMG-reductase inhibitor is already known in the art, as taught by Yumibe et al. Tomiyama et al. teach modified beta-lactams comprising C-glycosides which are improved over Yumibe's O-glycosides, as discussed above. One of ordinary skill in the art could have substituted Tomiyama's modified beta-lactams for the beta-lactams in the combination taught by Yumibe et al. and would have predicted that the resulting composition would be effective for reducing plasma cholesterol levels and treating atherosclerosis.

Further, both cholesterol biosynthesis inhibitors and the β-lactams taught by Tomiyama et al. are known

in the art for reducing serum cholesterol levels. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Response to Arguments

Applicant argues that the combination of the compound of claim 4 and HMG-CoA reductase inhibitor displays a greater synergistic effect than would be expected in view of the prior art, and that the combination is effective for lowering serum cholesterol levels. The declaration of Kazuhiro Kosakai submitted October 26, 2009 shows that the claimed compound in combination with either atorvastatin or rosuvastatin shows a greater synergistic effect than the combination of the prior art compound 56 with the same statins. However, this data is not commensurate in scope with the claims, which are drawn to any HMG-CoA reductase inhibitor or one of many recited in claim 29. See MPEP 716.02(d): Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing the unexpected results must be reviewed to see if the results occur over the entire claimed range. In this case, statins are known to have different pharmacological effects and drug interactions. Please see the Bellosta reference, attached herein for Applicants convenience. Thus, the results presented in the Kazuhiro Kosakai could not be reasonably expected to occur over the entire claimed range of HMG-CoA reductase inhibitors. For this reason, the rejection is maintained."

With regard to claim 29, Applicants respectfully submit that cancellation of that claim renders the rejection thereof moot.

As to the rejection of claim 4, Applicants respectfully traverse the rejection thereof because a prima *facie case* of obviousness has not been established with respect to the claim as amended herein.

The Federal Circuit has ruled that a *prima facie* case of obviousness must establish: (1) some suggestion or motivation to modify the references; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Feb. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970). Applicants note that the "teaching-suggestion-motivation" test for obviousness is still applicable following the Supreme Court decision in KSR International Co. v. Teleflex Inc. 550 U.S. - , 82 USPQ2d 1385 (2007) and that there is no teaching, suggestion or motivation in the cited references to induce one of ordinary skill in the art to derive the present invention. A *prima facie* case of obviousness must also include a showing of the reasons why it would be obvious to modify the references to produce the present invention. See Ex parte Clapp, 277 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). The examiner bears the initial burden to provide some convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings. Id. at 974.

The examiner cites Yumibe, et al., U.S. Pat. No. 5,756,470, as teaching a combination of a cholesterol biosynthesis inhibitor, specifically HMG-CoA reductase inhibitors, and a beta-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis. The examiner further

cites Tomiyama, et al., U.S. Published Application No. 2004/0063929, as teaching the beta-lactam compound of the instant claim 4 as a useful serum cholesterol lowering agent which is stable to metabolism by glycosidase and hydrolysis.

However, the examiner acknowledges that Tomiyama, et al. do not teach the combination of the beta-lactam compound and a cholesterol biosynthesis inhibitor, much less the beta-lactam compound of claim 4 in combination with an HMG-CoA reductase inhibitor. Instead, the examiner contends that such a combination would be obvious to one of ordinary skill in the art.

The examiner further contends, in the response to Applicants' previous arguments, that statins are known to have different pharmacological effects and drug interactions, citing the Bellosta reference, but notes that Applicants' objective evidence presented in the declaration of Kazuhiro Kosakai is not commensurate in scope with the claims in that the results presented therein could not be reasonably expected to occur over the entire claimed range of HMG-CoA reductase inhibitors.

Claim 4 as presented herein recites a specific composition as a serum cholesterol lowering agent or preventive or therapeutic agent for atherosclerosis which comprises the combination of the C-glycoside beta-lactam compound 56 of Tomiyama, et al., and an HMG-CoA reductase inhibitor selected from the group consisting of atorvastatin and rosuvastatin. Thus, the scope of this claim is now commensurate with the data

provided in the declaration of Kazuhiro Kosakai. As pointed out therein, this combination displays a significant pharmacologically synergistic effect with respect to the lowering of serum cholesterol that is not suggested by the use of either component individually, nor by the teaching of Yumibe, et al. or Tomiyama, et al., individually or in combination.

Furthermore, this synergistic effect of the combination of the recited beta-lactam compound and the specified HMG-CoA reductase inhibitors on the lowering of serum cholesterol cannot be expected from the teaching of the Bellosta reference which is directed to the adverse effects of the interaction of statins with pharmaceuticals other than beta-lactam cholesterol absorption inhibitors. Indeed, nothing in Bellosta refers to any positive synergistic effect obtained with statins in combination with any other pharmaceutical, and certainly not with O-glycoside beta-lactams or C-glycoside beta-lactams.

Accordingly, Applicants respectfully submit that the Examiner's reference to Bellosta is of no value in the present application.

Furthermore, neither Yumibe, et al. nor Tomiyama, et al. provide a teaching of the combination of the C-glycoside beta-lactam cholesterol absorption inhibitor of Compound 56 of Tomiyama, et al., with the HMG-CoA reductase inhibitors atrovastatin and/or rosuvastatin or suggest that such a combination, or any beta-lactam/HMG-CoA reductase inhibitor

combination, would exhibit the pronounced synergistic effect on the lowering of serum cholesterol obtained by the present invention.

In view of the complex and multifaceted process of cholesterol absorption which takes place in the body and which is duly noted by Davis, U.S. Pat. No. 5,661,145, cited by the Examiner in the office action of April 23, 2009, (Col. 1, lines 43-44), Applicants respectfully submit that a teaching of reduction of plasma cholesterol by a combination of one specific HMG-CoA reductase inhibitor (lovastatin in Davis) and one specific series of beta-lactam compounds which is completely different from that of the present invention, or the teaching of adverse drug interactions not involving beta-lactam compounds as in Bellosta, would not lead one to expect the synergistic effect on the lowering of serum cholesterol levels by the combination of specific HMG-CoA reductase inhibitors and a completely different series of beta-lactam compounds as recited in claim 4 and demonstrated by the Kosakai declaration.

Prior to the present application, there was nothing to suggest that a combination of C-glycoside beta-lactams and HMG-CoA reductase inhibitors selected from the group consisting of atorvastatin and rosuvastatin would have a synergistic effect with respect to serum cholesterol levels.

This synergistic effect of the combination of claim 4 herein is clearly shown by the data presented in Table 13 of the present

application. In Table 13, the beta-lactam compound is the compound 56 of Tomiyama, et al., as recited in claim 4 and the HMG-CoA reductase inhibitor is atrovastatin.

As seen in Table 13, a combination prescription of compound 56 administered at 0.3 mg/kg/day with atrovastatin administered at 1 mg/kg/day lowered serum cholesterol in the test animals by 20.2%. In contrast, use of compound 56 alone at the same dosage lowered serum cholesterol by only 6.9% while atrovastatin alone at the same dosage lowered serum cholesterol by only 6.2%. Clearly when used together, the C-glycoside beta-lactam compound 56 and the HMG-CoA reductase inhibitor complement each other and produce a significant pharmacologically synergistic effect on the lowering of serum cholesterol. Such a synergistic effect between a C-glycoside beta-lactam compound and HMG-CoA reductase inhibitor on the lowering of serum cholesterol levels is not taught or suggested by Yumibe, et al. or Tomiyama, et al. or Davis or Bellosta.

Furthermore, the examiner's reliance on Yumibe, et al. as teaching the combination of an O-glycoside beta-lactam and an HMG-CoA reductase inhibitor to show that it would be obvious to substitute the C-glycoside beta-lactam of Tomiyama, et al. is, respectfully, misplaced.

Although Yumibe, et al. disclose the use of an HMG-CoA reductase inhibitor with a beta-lactam compound, as has previously been pointed out, like Davis, the beta-lactam of

Yumibe, et al. is a different class of compound, i.e., an O-glycoside beta-lactam, having a different mode of activity than the beta-lactam of the present invention, which is a C-glycoside beta-lactam. There is no teaching in Yumibe, et al. to suggest a synergistic activity between the O-glycoside beta-lactam of the reference and the listed HMG-CoA reductase inhibitors much less between the C-glycoside beta-lactam of Tomiyama, et al., and the HMG-CoA reductase inhibitors as recited in claim 4 of the present invention.

The only pertinent discussion in Yumibe, et al. concerning the use of an HMG-CoA reductase inhibitor is the brief mention at column 2, lines 11-20 that "Combination therapy of an HMG-CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patient than either agent in monotherapy". However, neither the O-glycoside beta-lactam of Yumibe, et al. nor the C-glycoside beta-lactam of Tomiyama, et al. or the present invention are considered to be bile acid sequestrants, the beta-lactams and the bile acid sequestrants have completely different mechanisms of operation. Accordingly, the teaching of Yumibe, et al. relating to a synergistic effect of HMG-CoA reductase inhibitors and bile acid sequestrants is not relevant to the combination of the C-glycoside beta-lactam of compound 56 and the HMG-CoA reductase inhibitors recited in claim 4.

Furthermore, the fact that Yumibe, et al. teach the combination of an O-glycoside beta-lactam with an HMG-CoA reductase inhibitor is not transferable to the Tomiyama, et al. teaching of the C-glycoside beta-lactam compound as there is nothing in Tomiyama, et al. to suggest a combination of that beta-lactam with another cholesterol inhibiting compound, nor that any appreciable synergistic effect would be expected.

As evidence of the unexpected pharmacological effect obtained by the combination of the C-glycoside beta-lactam compound 56 and specific HMG-CoA reductase inhibitors over similar combinations of C-glycoside beta-lactams and HMG-CoA reductase inhibitors or the respective beta-lactams and HMG-CoA reductase inhibitors alone, Applicants presented the previously filed Declaration of Kazuhiro Kosakai, showing the effect of such compounds and combinations on levels of serum LDL and HDL cholesterol.

As is readily evident from the results provided in Tables 1 and 2 of the declaration, the effect of the combination of compound 56, the C-glycoside beta-lactam recited in Claim 4 of the present invention, and the HMG-CoA reductase inhibitors atorvastatin and rosuvastatin is significantly greater than that observed with compound 56 alone. In addition, when compared with corresponding combinations of an O-glycoside beta-lactam, compound A in the experiments of the Declaration, and the same HMG-CoA reductase inhibitors, Applicants' combination of compound

56 and HMG-CoA reductase inhibitors exhibits a greater synergistic effect.

Thus, even if Yumibe, et al. did teach a synergistic effect between O-glycoside beta-lactams and HMG-CoA reductase inhibitors, which the reference clearly does not do, the significant improvement in such effect obtained using the C-glycoside beta-lactam compound of Tomiyama, et al. would not be obvious as there is nothing to teach substitution of a C-glycoside beta-lactam for the O-glycoside beta-lactam of Yumibe, et al.

Furthermore, even if one did make the substitution, for which there is no suggestion in the prior art, one would only expect the same level of synergistic effect obtained using the O-glycoside beta-lactam, not the enhanced effect evidenced by Applicants' combination of the C-glycoside beta-lactam compound 56 and the specifically recited HMG-CoA reductase inhibitors.

In view of the foregoing, Applicants respectfully submit that it would not be obvious to one of ordinary skill in the art, knowing the action of the compounds of Yumibe et al. to expect the improvements exhibited by combining the cholesterol biosynthesis inhibitors of Yumibe et al. with the C-glycoside beta-lactams of Tomiyama et al. Furthermore, there is nothing to suggest that a substitution of C-glycoside beta-lactams for the different series of beta-lactams in Yumibe, et al. would result in a similar improvement in the effect on cholesterol reduction.

Bellosta does not even mention a combination of HMG-CoA reductase inhibitors with beta-lactam compounds. Because the actions of the beta-lactams of the respective references are different, Applicants respectfully submit that there is nothing in the prior art references to support the combination thereof as urged by the examiner and that a *prima facie* case of obviousness has not been established.

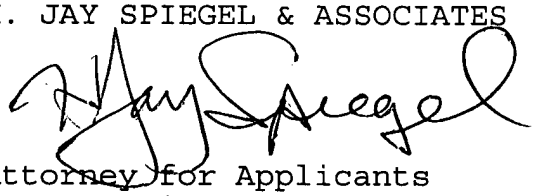
Accordingly, Applicants respectfully submit that the present rejection under 35 U.S.C. 103(a) is without support and should be withdrawn.

Although this Amendment is presented after a Final Rejection, it is submitted that it should be entered. The Amendment reduces the issues that would be present upon Appeal by canceling Claim 29 and by amending independent Claim 4 to render its scope commensurate with the evidence provided in the previously filed Declaration of Kazuhiro Kosakai. The prosecution of this application has been lengthy and Applicants submit that the most pertinent prior art is already of record. The amendments set forth herein do not necessitate further consideration or search on the part of the Examiner. For all of these reasons, it is submitted that the Amendment should be entered at this time even if the Examiner does not intend to allow the application. Such entry would, again, reduce the issues that would be present on Appeal. Accordingly, entry of the Amendment is respectfully solicited.

In view of the foregoing, Applicants respectfully submit that the claims as amended herein are allowable over the prior art and entry of the Amendment and mailing of a notice of allowance are respectfully requested.

Respectfully submitted,

H. JAY SPIEGEL & ASSOCIATES



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